Global Regulatory Policy

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July 21, 2004

Division of Dockets Management
U.S. Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. 2003N-0342 Toll-Free Number for Reporting Adverse Events on Labeling for Human Drug Products, Proposed Rule

Merck & Co., Inc. (Merck) is a leading worldwide, human health products company. Through a combination of the best science and state-of-the-art medicine, Merck's research and development pipeline has produced many important pharmaceutical products available today. These products have saved the lives of or improved the quality of life for millions of people globally.

As a leading pharmaceutical company, Merck has extensive experience in thoroughly evaluating our products from discovery to approval and throughout their marketing life to ensure that they continue to provide health benefits with minimum risk. Therefore, we are well qualified to comment on the above referenced proposed rule (69 FR 21778).

Merck appreciates the opportunity to comment on this proposed rule and welcomes the chance to work with the Food and Drug Administration (FDA). Please find below our general comments regarding the adverse event reporting process, the integrity of the MedWatch data, and Congressional intent regarding Section 17 of the Best Pharmaceuticals for Children Act (BPCA). We also provide more specific comments that address particular sections of the proposed rule.

General Comments

Merck supports the Agency's effort to implement Section 17 of the BPCA. We commend the FDA on its decision not to include modifications to the requirements for physician labeling at this time. We agree that while physician labeling is available to consumers in the Physician Desk Reference (PDR), it is not intended or written for a consumer or patient audience. Additionally, since the proposed rule will require pharmacies to distribute the "side effects" statement to consumers who fill a new prescription or refill an existing prescription, changing the physician labeling to include information intended for consumers at this time would be redundant.

We also support the Agency's decision not to include modifications to the requirements for patient package inserts (PPIs) in this proposed rulemaking. As stipulated in the proposed regulation, drug products that are accompanied by PPIs are dispensed by pharmacists, and the statement will therefore be provided to consumers per the provisions of the proposed rule.

However, as outlined below, we are concerned about the following aspects of this rulemaking and its affect on the FDA's mission to protect the public health.

Adverse Event Reporting Process and MedWatch Data Integrity

As proposed, the rule will encourage consumers to file adverse event reports (AERs). Patients may submit AERs to the FDA and the company, while they may also seek medical advice from their doctor. This has the potential to result in multiple adverse event reports for the same adverse event, which will increase the total number of duplicate AERs. The increase in the number of duplicate adverse event reports may make it more difficult to detect true AEs as the information in the AER database is no longer reliable or valid.

Additionally, when duplicate AERs are submitted, it will frequently be difficult for sponsors to determine whether the line listings and/or sanitized reports received from the Agency are in fact duplicative of reports submitted to the company, which will further complicate our ability to detect potential safety and quality issues. This situation is consistent with our experience at present in which duplicate information is provided to the manufacturer and to the MedWatch database.

The proposed rule may also reduce the effectiveness of the Agency's adverse event reporting program because reports of side effects for marketed products that otherwise would be directed to the company, and subsequently reported to FDA, may be directly reported to the Agency. Merck currently monitors telephone calls received from consumers regarding marketed products. This facilitates the reporting of adverse events to the FDA and allows a rapid response to potential product quality or safety issues. Under the Agency's proposed system, telephone calls from consumers that might be directed to drug manufacturers may be diverted to FDA's voluntary MedWatch number. This may increase the possibility of a consumer's exposure to potential product quality or safety issues (e.g., tampering situations) prior to notifying the manufacturer. Additionally, consumers may not submit the completed side effects report to the Agency in a timely manner, further delaying the inclusion of the AE into the database.

Moreover, under the present system, while consumers can report adverse events to the Agency, doctors or other health care professionals generally act as intermediaries between patients, the Agency, and the pharmaceutical industry. It is the health care professionals who can best explain the adverse event, the patient's medical history, and other concomitant therapies, and as such "validate" the report.

Under the FDA's proposed system, in many cases, the loss of interaction with health care professionals will dilute the reliability and overall completeness of the information captured in the database.

Lastly, the current MedWatch form that will be sent to consumers to report side effects was created for people with medical knowledge and may be difficult for consumers to complete.

Recommendation: We recommend that the FDA develop a sorting and tracking method within the MedWatch database to distinguish AEs submitted by consumers from those submitted by other sources. This will help to ensure that adverse event report duplication is minimized and that the information maintained in the database is credible and useful.

Moreover, the Agency should modify the MedWatch Form to simplify reporting by consumers. A consumer-friendly form should include the following:

1. Text to clarify the definition of a side effect.
2. Specific sections that will enable patients to document underlying health conditions, as well as other medications the patient may be taking (including nutritional supplements).
3. A section that requests consumers to provide the contact information for his or her doctor. This will provide manufacturers and the Agency with a mechanism to request follow-up information from a health care professional.

Congressional Intent Regarding OTC Drugs

We believe the proposed rule extends the FDA's regulatory authority further than Congress originally intended by including changes to OTC labeling in the proposed rule. As written, section 17 of the BPCA requires the Secretary of Health and Human Services (HHS) to:

> *"...promulgate a final rule requiring that the labeling of each drug for which an application is approved under section 505 of the Federal Food, Drug, and Cosmetic Act...include the toll-free number maintained by the Secretary for the purpose of receiving reports of adverse events regarding drugs and a statement that such number is to be used for reporting purposes only, not to receive medical advice."*

While this can be interpreted that the final rule should include all drug products, we believe Congress' intent was to limit the labeling requirements to prescription drug products only. If Congress originally intended to include OTC drugs, it seems illogical that the statute would only require products approved under section 505 of the Act, since the vast majority of OTC products are marketed under their respective OTC monographs and would be excluded from meeting this requirement. Thus, if the wording in the proposed rule is published as final, only a fraction of OTC products would be required to

comply, creating inequities on the labels of marketed OTC products and the potential for confusion among consumers regarding the use of the toll-free number for some OTC products but not others. Furthermore, the BPCA does not specifically mention OTC drug products or the cost to the OTC drug industry, nor does the BPCA's legislative history address the mandatory inclusion of the phone number with all OTC drug products, the mechanics of changing the OTC label, or the cost to implement the labeling change to the OTC drug industry. In fact, Congress is currently developing legislation to define the adverse event reporting requirements for OTC drugs and dietary supplements (the bill is being developed by Senators Orrin Hatch (R-Utah), Tom Harkin (D-Iowa) and Richard Durbin (D-Illinois)[1]). Therefore, an additional requirement for OTC products approved under section 505 creates unnecessary confusion and redundancy.

Recommendation: We recommend that FDA interpret the wording in the BPCA in a manner more consistent with Congress' original intent such that OTC drug products are not included in the Agency's final rulemaking. We further recommend that FDA revise the proposed rule to apply the toll-free number labeling requirement exclusively to medication guides for prescription drugs.

Specific Comments

D. Specific Proposed Changes to the Regulations

1. Side Effects Statement

We are concerned that the inclusion of an additional telephone number without clear instructions may be confusing for consumers. Currently, some of our drug products' labeling include a telephone number for consumers and health care professionals to contact us regarding questions. Additionally, OTC drugs for oral administration must bear a general label warning that, "In case of overdose, get medical help or contact a Poison Control Center right away." A similar warning is required for drugs not intended for ingestion that are swallowed. With the addition of another toll-free number on drug product labeling or accompanying materials, consumers could easily be confused by the inclusion of multiple phone numbers and instructions for use when experiencing an adverse event. In an emergency situation, a consumer might mistakenly contact FDA's toll-free phone number instead of a health professional with the hope of receiving medical advice or information. This could lead to injuries that may have been avoided if the appropriate health professional had been contacted promptly.

Recommendation: We recommend that FDA ensure that consumers are clearly informed of the purpose of the toll-free number for side effects. Specifically, FDA's "side effects" statement should include the statement: *"If you are experiencing a medical emergency, please contact your doctor, hospital, or other health professional."*

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[1] *Tan Sheet*. Volume 12, p. 7 (7/12/2004)

In addition, we recommend that the Agency revise the side effects statement to read: *"Please contact the FDA to report side effects only if there is no emergency, or, in the case of an emergency, after the emergency has been resolved."*

Also, we assume that when consumers call the FDA's toll-free number that they will encounter a recorded message that directs them to leave their name and address so that an Agency official can send them a side effects form, as opposed to consumers encountering a person that is "live" on the telephone. Therefore, we recommend that the recorded message include explicit instructions that direct consumers to contact their doctor or a hospital in case of a medical emergency. Including this information on the Agency's recording will aid in avoiding confusion that may occur due to the inclusion of multiple toll-free numbers listed on product labels.

V. Analysis of Economic Impacts

Section A.2.b; Cost to modify product labeling

We believe the FDA's estimate of the cost to the OTC industry is not accurate. In the proposed rule, the FDA estimated that approximately 522 over-the-counter (OTC) drug products would be affected by the labeling changes required by the regulation at a cost estimated to be $1.3-3.7M[2] . However, we would like to note that for each product marketed, there are multiple stock keeping units (SKUs). As a result, there may be well in excess of 1,000 branded packages ultimately affected by the rulemaking. We estimate that it will cost drug manufacturers approximately $12,000 to make changes to a single OTC product label. Based on this estimate, it will cost drug manufacturers at least $12 M to change the labels of the conservatively estimated 1,000 branded packages that will be affected by this rulemaking.

Section A.3; Burden on FDA

With regard to OTC products, we would like to caution FDA that the potential exists for MedWatch to receive tens of thousands of calls from consumers dissatisfied with a product for a variety of reasons, some of which may not be safety related. Merck receives approximately 40,000 calls per year from consumers. It is our experience that only 12% of consumer telephone calls are related to AEs while the majority are for other reasons, such as information inquiries, requests regarding patient assistance programs, product quality complaints, and to provide feedback. An exponential increase in call volume could divert resources from the principal MedWatch goal of receiving and monitoring adverse event reports from physicians.

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[2] 69 *Federal Register* 21788

Conclusion

In summary, careful consideration must be given to maintaining the value of the MedWatch system. Additionally, the FDA should not include OTC drug products in the Final Rule for the reasons previously articulated.

The Agency should also take the necessary steps to make it explicitly clear to consumers that its toll-free number is merely a reporting mechanism, not a system to report medical emergencies or obtain medical advice.

If we can provide further assistance, please do not hesitate to contact Brian Mayhew, Regulatory Policy Analyst, at 301-941-1402.

Respectfully submitted,

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